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# A Cost-Effectiveness Analysis of Eletriptan 40 and 80 mg versus Sumatriptan 50 and 100 mg in the Acute Treatment of Migraine

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## ABSTRACT

**Objectives:** This article explores the application of cost-effectiveness analysis in a comparison of eletriptan and sumatriptan in the acute treatment of migraine.

**Methods:** The study employs data from a randomized, double-blind, placebo-controlled clinical trial comparison of oral eletriptan (40 and 80 mg) and oral sumatriptan (50 and 100 mg). Analyses were undertaken using two composite measures of treatment outcome constructed to reflect the requirements of patients more comprehensively than the conventional efficacy indicator of headache response at 2 hours. On the cost side of the equation, reflecting the health-care system perspective of the analysis, drug costs for initial dosing, second dosing for non-response, and recurrence and rescue medication were taken into account.

**Results:** The analysis found that eletriptan treatment resulted in lower costs per successfully treated attack than those of sumatriptan under both outcome criteria.

**Conclusion:** Further refinement of outcomes measurement in migraine would be valuable and eletriptan has a potentially important role to play in the cost-effective management of the disorder.

*Keywords:* cost-effectiveness, economic evaluation, eletriptan, migraine, sumatriptan.

## Introduction

The arrival during the 1990s of a new, specific class of medicines for treating acute migraine attacks (the serotonin 5-$HT_{1B/1D}$ receptor agonists) has given rise to considerable interest in the economics of migraine and its management. Early pharmacoeconomic research in this area concentrated on the cost of the illness [1–4]. These studies revealed a general pattern of relatively low direct care costs but substantial indirect costs attributable to absence from, or reduced effectiveness at, work during migraine attacks [5,6]. This information has played an important role in raising professional and public awareness of the disorder, identifying the significant drivers of cost and in enabling comparisons to be made with the burdens of other diseases. However, cost-of-illness data are of little help in guiding efficient health-care resource allocation [7,8]. These data only establish current levels of resource consumption without demonstrating whether they are appropriate or if further resources should be directed to the management of the disorder in question. Decision making in this regard should be informed by the cost-effectiveness of available treatment options, not by the cost of the disease [9].

The shifting balance now emerging in the literature away from cost of migraine studies toward treatment-specific economic evaluations is consequently a positive development. It is also timely given the increasing emphasis health authorities are placing on maximizing the return, or health gain, from available health-care resources. However, the evaluations currently being reported frequently pursue different objectives in a variety of care settings while employing differing methodologies and end points [10–18]. Clinicians and other decision makers are therefore able to draw on a growing volume of information about the value of specific treatment

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options but often find it difficult to compare the results generated by the different studies. Against this background and given the increasing number of antimigraine treatments becoming available for prescription use, a more consistent approach to evaluation would be helpful.

Cost-effectiveness analysis is a technique of economic evaluation that facilitates comparisons of the costs and outcomes of health-care interventions. It could therefore provide a useful framework for examining the value-for-money characteristics of competing antimigraine therapies [19]. This article explores the application of this methodological approach in a comparison of the cost-effectiveness of oral sumatriptan, the first-launched and currently most widely prescribed serotonin 5-$HT_{1B/1D}$ agonist for treating migraine attacks, with eletriptan, a more recent innovation in this class of agents.

## Methods

The cost-effectiveness analysis was based on data gathered in a randomized, double-blind, double-dummy, placebo-controlled Phase III clinical trial comparing two doses of oral eletriptan (40 and 80 mg) and two doses of oral sumatriptan (50 and 100 mg) in the treatment of migraine [20]. Although not designed primarily for economic evaluation, the study had collected sufficient data to form the basis of a cost-effectiveness analysis. An analytical framework was therefore established a priori and subsequently applied to the clinical trial data set.

The clinical trial extended over three attacks (or for a maximum of 12 weeks) but only the first of these was employed for the cost-effectiveness analysis. This approach not only simplified the analysis, it also maximized the number of patients available for inclusion in the economic evaluation. By focusing on the initial attack only, any problems potentially linked to some patients subsequently deciding not to continue to participate in the clinical trial were avoided. In addition, confining attention to the first attack meant that treatment responses would not be influenced by prior exposure to the two medicines. The exclusion criteria for the clinical trial required that patients should not previously have used either eletriptan or sumatriptan. Finally, reassurance that the first attack is representative can be drawn from evidence about consistency of response. The conventional 2-hour headache response rates in the first attack were within 2.5% of the average for all three attacks for eletriptan 40 mg and both dosage strengths of sumatriptan. For eletriptan 80 mg, the corresponding response rate was 3.2% less than the three-attack average.

**Table 1** Treatment sequences for the first attack

| Treatment sequence | First dose | Second dose |
|---|---|---|
| 1 | Eletriptan 40 mg | Eletriptan 40 mg |
| 2 | Eletriptan 40 mg | Placebo |
| 3 | Eletriptan 80 mg | Eletriptan 80 mg |
| 4 | Eletriptan 80 mg | Placebo |
| 5 | Sumatriptan 50 mg | Sumatriptan 50 mg |
| 6 | Sumatriptan 100 mg | Sumatriptan 100 mg |
| 7 | Placebo | Placebo |

During the attack, patients were randomized to one of the seven treatment sequences shown in Table 1. A treatment sequence consisted of an initial dose to be taken following the onset of migraine with headache of severe or moderate intensity. The second treatment in the sequence could be taken if there was a lack of response 2 hours after the initial dosing, that is, if headache had failed to ameliorate to mild or resolve completely to pain-free from the baseline status of either severe or moderate. Rescue medication was allowed from 2 hours after this second dose if required. A second dose of the study drugs was also permissible if the headache, having initially responded positively by 2 hours, recurred with moderate or severe intensity within a period of 24 hours from the first treatment.

For the purpose of this cost-effectiveness study, only those eletriptan treatment sequences in which active drug was available throughout the attack were compared with the sumatriptan arms of the trial. Patients who were randomized to treat the attack with eletriptan 40 mg or eletriptan 80 mg as a first dose and who would then have received, if required, placebo as a second dose for either nonresponse or headache recurrence have therefore been excluded. Patients randomized to these active drug/placebo sequences have been excluded from the analysis even if they only required the first dose to manage the migraine attack. Such sequences, although relevant to a Phase III trial assessing the efficacy and safety of a second dose, would not be employed in the management of migraine in clinical practice. In the sumatriptan 50 and 100 mg groups, all patients received, if required, sumatriptan 50 or 100 mg as the second dose, respectively.

In the following sections, the notation E40/E40 refers to patients who were randomized to the treatment sequence in which eletriptan 40 mg was used as the first dose and was also available, if needed, as the second dose for treating either nonresponse or recurrence. The notation E80/E80 applies in a cor-

responding way to eletriptan 80 mg. Finally, S50/S50 and S100/S100 refer to the sumatriptan 50 and 100 mg treatment sequences, respectively.

### *Outcomes*

In cost-effectiveness analysis, it is important that the outcome chosen (that is, the measure of treatment success) is of relevance to the patient. Clinical studies of migraine therapies have almost universally employed headache response at 2 hours after initial dosing as the primary indicator of treatment efficacy [21]. Specifically, assessment has centered on the percentage of patients improving from severe or moderate headache at baseline to mild headache or no pain at 2 hours. By itself, however, this measure has limited clinical meaning and only partially reflects what may be important to migrainers. It fails to differentiate, for example, between treatments generating a substantial improvement in migraine headache from severe at the start of treatment to pain-free 2 hours later and those only ameliorating the pain from moderate to mild over the same time period. In addition, effective treatment will embrace, from the patient's perspective, characteristics other than just headache response at 2 hours—such as the speed with which pain relief is obtained and normal functioning can be resumed as well as the likelihood of headache recurrence. A quicker and sustained response also has economic implications: for example, an individual suffering a migraine attack may be less likely to cease work if she or he begins to feel better after a short period of time.

The primary clinical trial efficacy end point—headache response at 2 hours—may therefore be argued to be too narrow a definition of treatment success for incorporation into a cost-effectiveness analysis. The present study consequently proposes and utilizes two alternative and more comprehensive measures of outcome. Both are composite in nature and are feasible because patients recorded their headache status at multiple time points during the clinical trial—immediately prior to first dosing and then at 0.5, 1, 2, 4, and 24 hours after treatment—as well as information about recurrence and the use of rescue medication.

The first of these measures identifies successful treatment as the achievement of pain-free headache status at 2 hours, no recurrence within 24 hours of the first dosing, and no requirement for rescue medication (pathways 1, 3, 14, 16, 27, and 29 in Fig. 1). This definition of successful treatment has the same construction as "sustained pain-free" [22]—which is attracting increasing interest among those investigating migraine treatments—but will be referred to as success measure 1 (SM1) in the present analysis. The second and more demanding outcome measure constructed for the cost-effectiveness analysis, hereafter designated SM2, defines successful treatment as a positive headache response at 1 hour, that is, an improvement from severe or moderate at baseline to mild or better, followed by the achievement of pain-free status by 2 hours, which is sustained at 4 hours and the absence of headache

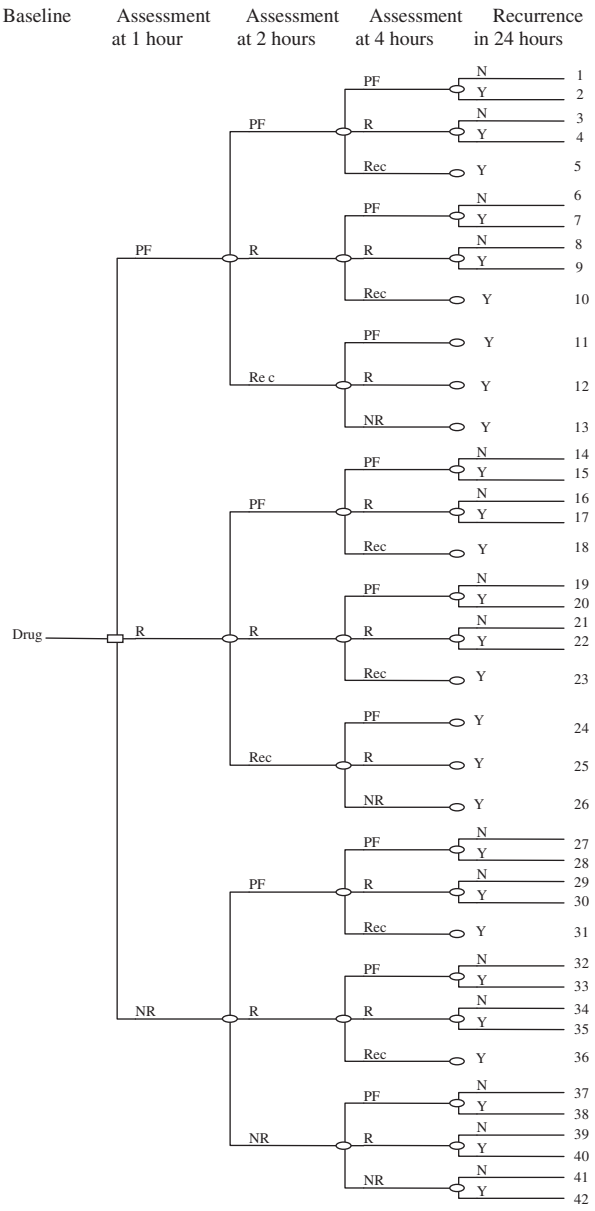


**Figure 1** A framework for assessing the outcomes of treating a migraine attack. PF, pain-free; R, response; NR, nonresponse; Rec, recurrence; N, no; Y, yes.

recurrence within 24 hours of the first dose (pathways 1 and 14 in Fig. 1).

With each of the definitions of successful treatment, attacks were classified into one of three categories. An attack was defined as successfully treated if all of the relevant assessments at the time points specified above were available and if the outcomes satisfied the definitions for success at each of these time points. An attack was classified as not successfully treated if any one of the assessments required for an outcome was negative, that is, did not meet the criteria for successful treatment. It should be noted that classification into this category does not require the availability of all time point assessments. Focusing on SM2, for example, a patient whose 1 hour assessment was missing but who was otherwise a pain-free responder at 2 and 4 hours until experiencing a recurrence within 24 hours of first dose would have had her/his attack classified as not successfully treated because the recurrence would have been sufficient to result in classification in this way.

An attack was classified as not evaluable if any of the assessments required to determine treatment outcome was missing, all other available assessments each individually satisfying the definition of successful treatment. For example, under SM2, a patient with a missing assessment at 1 hours, who was pain-free at 2 and 4 hours, with no headache recurrence within 24 hours of first dose would have had the attack classified as not evaluable. Attacks were also classed as not evaluable if baseline headache severity was not rated as either moderate or severe.

### *Costs*

Reflecting the health-care system perspective of the analysis, the cost side of the cost-effectiveness equation comprises the costs of all headache medications used by patients up to 24 hours after first dose for those who did not experience headache recurrence and up to 24 hours after treatment for recurrence for those patients who did recur. It includes both study drugs and rescue medication. For sumatriptan, the cost for each dose was calculated as a simple mean of the prices of individual tablets in the 6 and 12 tablet packs for the 50 mg dose and in the 6 and 12 tablet packs for the 100-mg dose. These data were taken from the March 2002 edition of the British National Formulary [23] and reflect net prices to the UK National Health Service. Following this approach, the prices employed in the study were £4.83 for the 50-mg tablet of sumatriptan and £8 for the 100-mg dose. For eletriptan, the price to the UK NHS is £3.75 for the 40-mg tablet, implying a cost of £7.50 for an 80-mg dose.

The costs of rescue medication used by patients in the study are difficult to estimate with accuracy. The case report forms used in the clinical trial only recorded the name of medication employed for rescue and did not provide any information about dosage. In addition, rescue medications, both single and combination compounds, were often recorded generically and precision in costing is not possible because the identity of the medicine supplier is unknown. These difficulties are further exacerbated by the fact that the study was conducted in 15 countries. Against this background, it was decided that an average cost per rescue medication usage would be derived rather than attempt to cost each individual drug employed for this purpose.

From the rescue medications listing, attention was focused on those medicines employed on five or more occasions. For each of these, the average dose recommended in the British National Formulary [23] and its net price to the UK NHS was obtained. This information was combined with the frequency with which each of these particular medicines was used, as recorded in the rescue medications listing, and the products summed to yield a weighted average cost per unit of rescue medication. This methodology resulted in an average cost of just £0.07 per usage of rescue medication, indicating that the choice of approach to estimating this cost component will have little impact on the study results.

The costs of other elements of health-care resource utilization associated with the management of migraine were not gathered in the clinical trial and have not been included in the cost-effectiveness analysis. However, the exclusion of these other expenditures does not devalue the cost-effectiveness analysis reported here because medicines are a significant component of migraine management costs and an increasing number of agents has become available in recent years. A study for the Office of Health Economics in the early 1990s found that prescription pharmaceuticals accounted for 68% of total NHS costs for migraine [24]. A corresponding proportion of 41% was reported for the Netherlands [25].

Finally, the cost per successfully treated attack (CPSTA) for each of the four active medication dosages (eletriptan 40 and 80 mg, sumatriptan 50 and 100 mg) was derived by dividing the total cost of treating all evaluable attacks by the number of those successfully treated as defined by the two composite outcome measures described earlier. To test the

robustness of the results, sensitivity analysis was applied to the values for both outcomes and costs.

### *Statistical Methods*

The numbers of successfully treated attacks in the four treatment sequence groups were calculated and compared using logistic regression. This method was adopted because it is an efficient means of analyzing data presented as proportions and easily handles the case where four treatment groups need to be compared simultaneously. The logit of the proportion of successfully treated attacks was the response measure, with the treatment group fitted as a single categorical explanatory variable. The treatment groups' comparisons were E40/E40 versus S50/S50, E40/E40 versus S100/S100, E80/E80 versus S50/S50, and E80/E80 versus S100/S100. Adjustments for multiple comparisons were not made since the above were only performed to show that the benefit of eletriptan over sumatriptan with respect to the number of successfully treated attacks was consistent with the benefit already seen in the 2-hour headache response rate reported in the clinical trial.

The CPSTA was calculated for each of the four treatment sequence groups, for each success criterion, as previously defined. Ninety-five percent confidence intervals for the CPSTA for each treatment sequence group and treatment group comparisons were obtained using bootstrap techniques [26]. All four treatment comparisons were of interest; thus, no formal adjustment for multiple comparisons was performed since precise *P* values have been quoted to demonstrate the extent of statistical significance. However, for completeness, an adjustment for multiple comparisons using the Bonferroni method as a sensitivity analysis was undertaken. All statistical analyses were performed using SAS 6.12 statistical software.

## Results

The numbers of attacks classed as evaluable for each treatment sequence group under each success criterion are presented in Table 2: 97% and 96% of treated attacks were classed as evaluable for the analyses using success criteria SM1 and SM2, respectively. The number of attacks evaluable for the analysis using success criterion SM1 was slightly larger than the number evaluable using success criterion SM2. This is because the SM1 criterion used only the 2-hour assessment, while the SM2 criterion required assessments at 1, 2, and 4 hours, and therefore some attacks with missing 1- or 4-hour assessments that were classed as not evaluable under SM2 were classed as successfully treated under SM1.

**Table 2** Number of evaluable attacks under the two successful treatment criteria

| Treatment group | Total numbers of attacks treated | Evaluable for SM1* | Evaluable for SM2† |
|---|---|---|---|
| E40/E40 | 93 | 91 | 91 |
| E80/E80 | 83 | 80 | 79 |
| S50/S50 | 181 | 177 | 176 |
| S100/S100 | 170 | 165 | 162 |
| Total (%) | 527 (100) | 513 (97) | 508 (96) |

*Attacks successfully treated if pain-free at 2 hours with no subsequent recurrence and no use of rescue medication.
†Attacks successfully treated if respond at 1 hour and pain-free at 2 and 4 hours with no subsequent recurrence.

Only a small number of attacks were classed as nonevaluable because of missing assessments: 11 (2%) of 524 for SM1 and 16 (3%) of 524 for SM2. These proportions were consistent in each of the four treatment groups. Nonevaluable attacks have been omitted from the analysis because of the similar, relatively small numbers involved and because it is reasonable to assume that the reasons for the missing assessments were consistent across the four treatment groups and not due to any differences in treatment effects. Finally, an additional three attacks were classed as nonevaluable because baseline headache severity was not rated as moderate or severe.

Table 2 also shows that the number of attacks in each of the two treatment sequences involving eletriptan was about half that in the groups employing sumatriptan. This reflects the design of the clinical study whereby the comparison of treatment efficacy using the 2-hour headache response rate was to be based, for eletriptan, on the combined data from the two sequences where the same dose of the drug was given first (i.e., E40/E40 plus E40/placebo and E80/E80 plus E80/placebo). Summing in this way would yield similar numbers of attacks in each of the eletriptan-combined groups to those in the individual sumatriptan groups.

Table 3 presents the demographic distribution of the patients whose attacks were evaluable under each success criterion: in both instances, the four treatment sequence groups were fairly well matched with regard to gender and age.

For both success criteria, a greater proportion of successfully treated attacks occurred in the two eletriptan treatment groups than in the sumatriptan arms (Table 4). Using success criterion SM1, the E40/E40 and E80/E80 groups had 30 and

**Table 3** Distribution (%) of patients by gender and age group for each success criterion

| Treatment group: | Criterion SM1* (*N* = 513) | | | | Criterion SM2† (*N* = 508) | | | |
|---|---|---|---|---|---|---|---|---|
| | E40/E40 (*n* = 91) | E80/E80 (*n* = 80) | S50/S50 (*n* = 177) | S100/S100 (*n* = 165) | E40/E40 (*n* = 91) | E80/E80 (*n* = 79) | S50/S50 (*n* = 176) | S100/S100 (*n* = 162) |
| Gender | | | | | | | | |
| Male | 14 | 10 | 10 | 12 | 14 | 10 | 10 | 12 |
| Female | 86 | 90 | 90 | 88 | 86 | 90 | 90 | 88 |
| Age group (years) | | | | | | | | |
| <18 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| 18–29 | 17 | 28 | 25 | 22 | 17 | 27 | 25 | 23 |
| 30–45 | 57 | 48 | 53 | 52 | 58 | 48 | 53 | 52 |
| >45 | 26 | 25 | 22 | 26 | 25 | 25 | 21 | 25 |

*Attacks successfully treated if pain-free at 2 hours with no subsequent recurrence and no use of rescue medication.
†Attacks successfully treated if respond at 1 hour and pain-free at 2 and 4 hours with no subsequent recurrence.

33% of attacks successfully treated, respectively, compared with 12 and 15% of attacks in the S50/S50 and S100/S100 groups. All four comparisons between E40/E40 and S50/S50, E40/E40 and S100/S100, E80/E80 and S50/S50, and E80/E80 and S100/S100 were statistically significant ($P < .01$ for all comparisons).

With success criterion SM2, 18 and 22% of attacks managed with E40/E40 and E80/E80, respectively, were successfully treated, compared to 8 and 10% of those treated with S50/S50 and S100/S100. The differences between E40/E40 and S50/S50, between E80/E80 and S50/S50, and between E80/E80 and S100/S100 were all statistically significant ($P = .021$, $P = .003$, and $P = .016$, respectively). The difference between E40/E40 and S100/S100 was close to reaching statistical significance ($P = .082$).

When costs are taken into account, Table 5 shows that the two eletriptan treatment groups had a lower CPSTA than the two sumatriptan treatment groups under both success criteria. For SM1, the costs in the eletriptan 40- and 80-mg groups were £17.55 and £31.76, compared with estimates for sumatriptan 50 and 100 mg of £63.98 and £80.50, respectively ($P < .024$ for all comparisons). For SM2, the estimated CPSTA in the eletriptan 40 and 80 mg groups was £29.61 and £48.13 compared to corresponding costs in the sumatriptan 50 and 100 mg groups of £95.63 and £124.28, respectively (E40/E40 vs. S50/S50, $P = .013$; E40/E40 vs. S100/S100, $P = .009$; E80/E80 vs. S50/S50, $P = .067$; E80/E80 vs. S100/S100, $P = .035$).

If an adjustment for multiple treatment comparisons is made using the Bonferroni method, three of four comparisons for SM1 remain statistically significant at the 0.05 level. For SM2, the comparison of E40/E40 versus S100/S100 stays statistically significant at the .05 level, the comparison of E40/E40 versus S50/S50 approaches statistical significance (adjusted $P = .052$) but the comparisons of E80/E80 against the two sumatriptan sequences

**Table 4** Numbers of successfully treated attacks

| Success criterion | Treatment group | 2-hour headache response rates (%)* | Number of evaluable attacks | Number of successfully treated attacks† (%) | Treatment comparison | *P* value‡ |
|---|---|---|---|---|---|---|
| SM1§ | E40/E40 | 64 | 91 | 27 (30) | | |
| | E80/E80 | 67 | 80 | 26 (33) | E40/E40 vs. S50/S50 | <0.001 |
| | | | | | E40/E40 vs. S100/S100 | 0.007 |
| | | | | | E80/E80 vs. S50/S50 | <0.001 |
| | S50/S50 | 50 | 177 | 21 (12) | E80/E80 vs. S100/S100 | 0.002 |
| | S100/S100 | 53 | 165 | 25 (15) | | |
| SM2‖ | E40/E40 | 64 | 91 | 16 (18) | | |
| | E80/E80 | 67 | 79 | 17 (22) | E40/E40 vs. S50/S50 | 0.021 |
| | | | | | E40/E40 vs. S100/S100 | 0.082 |
| | | | | | E80/E80 vs. S50/S50 | 0.003 |
| | S50/S50 | 50 | 176 | 14 (8) | E80/E80 vs. S100/S100 | 0.016 |
| | S100/S100 | 53 | 162 | 16 (10) | | |

*Percentage of attacks improving from severe or moderate at baseline to mild or pain-free at 2 hours.
†Attacks successfully treated according to the relevant criteria SM1 or SM2.
‡Based on logistic regression model with treatment as the single explanatory variable.
§Attacks successfully treated if pain-free at 2 hours with no subsequent recurrence and no use of rescue medication.
‖Attacks successfully treated if respond at 1 hour and pain-free at 2 and 4 hours with no subsequent recurrence.

**Table 5** Cost per successfully treated attack (CPSTA)

| Success criterion | Treatment group | Total number of doses of study medication used by evaluable subjects | Total number of rescue medications used by evaluable subjects | Number of successfully treated attacks* (%) | Total cost of treatment (£) | CPSTA (£) (95% CI) | Treatment comparison | *P* value | Adjusted *P* value† |
|---|---|---|---|---|---|---|---|---|---|
| SM1‡ | E40/40 | 126 | 18 | 27 (30%) | 473.76 | 17.55 (13.32–24.85) | | | |
| | E80/E80 | 110 | 11 | 26 (33%) | 825.77 | 31.76 (24.11–45.43) | E40/E40 vs. S50/S50 | <0.001 | 0.002 |
| | | | | | | | E40/E40 vs. S100/S100 | <0.001 | 0.002 |
| | | | | | | | E80/E80 vs. S50/S50 | 0.024 | 0.096 |
| | S50/S50 | 277 | 82 | 21 (12%) | 1343.65 | 63.98 (46.27–97.31) | E80/E80 vs. S100/S100 | <0.005 | 0.020 |
| | S100/S100 | 251 | 64 | 25 (15%) | 2012.48 | 80.50 (60.52–119.84) | | | |
| SM2§ | E40/40 | 126 | 18 | 16 (18%) | 473.76 | 29.61 (21.27–45.83) | | | |
| | E80/E80 | 109 | 11 | 17 (22%) | 818.27 | 48.13 (33.16–73.69) | E40/E40 vs. S50/S50 | 0.013 | 0.052 |
| | | | | | | | E40/E40 vs. S100/S100 | 0.009 | 0.034 |
| | | | | | | | E80/E80 vs. S50/S50 | 0.067 | 0.266 |
| | S50/S50 | 276 | 82 | 14 (8%) | 1338.82 | 95.63 (66.25–167.91) | E80/E80 vs. S100/S100 | 0.035 | 0.140 |
| | S100/S100 | 248 | 63 | 16 (10%) | 1988.41 | 124.28 (87.89–205.30) | | | |

*Attacks successfully treated according to the relevant criteria SM1 or SM2.
†*P* value adjusted for multiple comparisons using Bonferroni method.
‡Attacks successfully treated if pain-free at 2 hours with no subsequent recurrence and no use of rescue medication.
§Attacks successfully treated if respond at 1 hour and pain-free at 2 and 4 hours with no subsequent recurrence.

S50/S50 and S100/S100 become nonsignificant (adjusted $P = .266$ and .140, respectively).

## Discussion

The average cost-effectiveness ratios shown in Table 5 reveal an economic advantage for eletriptan over sumatriptan. Indeed, in most of the comparisons eletriptan is the dominant option since it is both more effective and less expensive than sumatriptan. In spite of the fact that this study was not powered to detect changes in these outcomes, only in the comparison of eletriptan 80 mg and sumatriptan 50 mg using the more demanding SM2 outcome measure is a statistically significant difference not quite achieved. Application of the Bonferroni adjustment results in a loss of statistical significance for E80/E80 versus S50/S50 under SM1 and for E80/E80 versus S50/S50 and S100/S100 using the SM2 criterion. The method is, however, conservative in that it errs on the side of nonsignificance [27]. Other less conservative methods for adjusting for multiple comparisons are available and would give different *P* values. The strength of the evidence and the conclusions regarding the relative benefit of eletriptan over sumatriptan are therefore best assessed using the mean CPSTA and the 95% confidence intervals that remain unchanged, regardless of the method used for adjusting for multiple comparisons.

The magnitude of this advantage is compelling but it remains important to ascertain the robustness of the results and this requires two key issues to be addressed. First, are the clinical trial findings utilized here sufficiently representative to provide the foundation for the cost-effectiveness analysis? Second, two alternative outcome measures were employed for the economic evaluation. It is clear, however, that many potential options exist and it is therefore important to establish that the SM1 and SM2 constructs are relevant and accord with current thinking in this area.

### *Representativeness of the Clinical Trial*

The conventional 2-hour headache response rates found in the clinical trial for eletriptan 40 and 80 mg and for sumatriptan 50 and 100 mg were 64, 67, 50, and 53%, respectively [20]. Broadening the perspective, a meta-analysis of the seven eletriptan phase II/III clinical studies conducted mainly in Europe and the United States found equivalent response rates of 60 and 66% for the 40- and 80 mg

**Table 6** Sensitivity analysis for SM1 treatment outcome results

| | Conventional 2-hour headache response rate (%) | | | SM1 success rates (%) | |
|---|---|---|---|---|---|
| Treatment | (a) This study | (b) Seven eletriptan studies (Pfizer, data on file)/Tfelt-Hansen [30] | % Difference between (a) and (b) | This study | Adjusted |
| E40 | 64 | 60 | −6.25 | 30 | 28 |
| E80 | 67 | 66 | −1.49 | 33 | 32 |
| S50 | 50 | 59 | +18.00 | 12 | 14 |
| S100 | 53 | 59 | +11.32 | 15 | 17 |

Note: The adjusted rates are derived by decreasing (for eletriptan) and increasing (for sumatriptan) the SM1 results by amounts that reflect the difference in the conventional 2-hours headache response rates in this specific study and in the overall eletriptan trial program (for eletriptan) and in the meta-analysis produced by Tfelt-Hansen [30] (for sumatriptan). It is assumed that there is consistency between the 2-hours headache response rate and the SM1 outcome measure.

doses, respectively (Pfizer, data on file). Focusing only on the three clinical studies in which sumatriptan was an active comparator, the corresponding eletriptan efficacy rates were 64 and 71%, respectively, while those for sumatriptan reached 53% for the 50-mg dose and 54% for the 100-mg dose [28].

Other clinical studies of sumatriptan—that is, investigations undertaken outside the eletriptan trial program—have reported a range of efficacy findings. A review by Tfelt-Hansen [29] of 12 placebo-controlled double-blind randomized clinical trials of sumatriptan 100 mg found a 2-hour headache response rate ranging from 46% to 67%. Combining the results of these published studies yielded an overall response rate of 58%. A more recently published review by the same author and colleagues [30] extended the coverage to 20 clinical investigations involving 3090 patients treated with sumatriptan 100 mg and calculated an almost identical combined 2-hour headache response rate of 59%.

The 50-mg dose of oral sumatriptan has been investigated to a lesser extent than its 100-mg counterpart. In their review published in 2000, Tfelt-Hansen and colleagues [30] identified seven relevant clinical trials. Based on a total of 1599 patients treated with the drug, the meta-analysis found a 2-hour headache response rate of 59%.

Assessing the representativeness of a single clinical study is not straightforward. Many variables might be compared. As well as the 2-hour headache response rate discussed above, attention might also be given to pain-free rates at 2 hours or other time points, therapeutic gain rates (calculated as the efficacy rate of the active agent minus that observed for placebo), and the incidence of recurrence. In addition, the number of attacks over which these variables might be studied and the differing ways in which the data might be analyzed give rise to further potential complexity. Nevertheless, the 2-hour headache response rate is the most widely used primary end point, and assuming there is consistency between it and the composite outcome measures underpinning the economic analyses reported in this article, the evidence suggests that the clinical trial supplying the data for the cost-effectiveness analysis can be considered to be broadly representative.

Furthermore, even if the composite treatment success rates employed in the cost-effectiveness analysis for eletriptan (Table 4) are reduced by an amount to reflect the slightly lower primary efficacy rates reported from the eletriptan trial program as a whole and, likewise, the sumatriptan success rates are increased to mirror the efficacy levels found by meta-analyses performed by Tfelt-Hansen et al. [30], the advantage of eletriptan over sumatriptan remains (Table 6). Employing the SM1 measure of outcome, the CPSTA for eletriptan is still less than 50% of that for sumatriptan (34% for eletriptan 40 mg and 45% for eletriptan 80 mg). Finally, taking costs into account, sensitivity analysis indicates that even with these revisions to treatment success rates, the prices for eletriptan—£3.75 for 40 mg and £7.50 for 80 mg—would have to rise substantially to generate the same CPSTA as sumatriptan. Thus, under SM1, the cost of eletriptan 40 mg would need to reach £10.95 per dose to achieve parity of CPSTA with sumatriptan 50 mg and that of eletriptan 80 mg would need to be £16.70 to result in the same CPSTA as sumatriptan 100 mg.

### *Definition of Treatment Success*

In recent years, there has been growing interest in measures of treatment outcome that are more comprehensive and meaningful to patients than the conventional efficacy end point of headache response at 2 hours [31]. In particular, considerable attention has been given to the concept of "sustained pain-free" which is defined as pain-free by 2 hours after dosing with no recurrence and no use of rescue medication 2 to 24 hours postdose [22]. This measure is increasingly being advocated by a number of opinion leaders and has recently been employed in a

meta-analysis of 53 trials of oral triptans in the acute treatment of migraine [31]. The SM1 outcome measure used in the cost-effectiveness analysis has the same construction as sustained pain-free and is therefore in line with current thinking in this area.

It should be noted that with both SM1 and sustained pain-free, instances of regression to mild headache without prompting further medication use are not counted as recurrences because they are not deemed to be clinically significant [32]. It is not clear, however, that such mild recurrences are truly insignificant from the patient's perspective. In reality, they might, for example, impose some limitation on the performance of usual activities. The outcome measure may be regarded as falling short of the "ideal" in a number of other respects. In a study by Lipton and Stewart [33], rapid onset of action was the third most frequently cited attribute of treatment regarded as very important by patients (following freedom from pain and the absence of recurrence). The second successful treatment criterion (SM2) employed in this article seeks to take this into account by incorporating an early indication of potential treatment effectiveness—that is, an improvement in headache to pain-free or mild pain at the 1-hour time point—into the outcome measure. This is clearly a much stricter test of effectiveness—for example, under SM2 attacks with a nonresponse at 1 hour would be deemed treatment failures even if they became pain-free at 2 and 4 hours with no recurrence or use of rescue medication—and is inevitably associated with marked reductions in treatment success rates.

Beyond these considerations, it is axiomatic that therapeutic success in migraine is not solely a function of the effectiveness or otherwise of treating headache. The occurrence of side effects and their tolerability should also be taken into account. The extent to which other symptoms associated with migraine such as nausea, photophobia, and photophonia are alleviated and the speed with which return to normal functioning is facilitated are additional factors that arguably should be incorporated into more comprehensive measures of treatment outcome in migraine. Alongside the implied requirement to continue to refine the content of migraine specific outcome measures—not only establishing the appropriate items but determining their relative weightings as well—attention also must be given to questions about the appropriate number of attacks over which treatment effectiveness should be evaluated and the settings in which such assessment should take place. Finally, while the nature of the clinical trial on which the present study has been based meant that only medication costs could be addressed, a truly comprehensive economic evaluation of the acute treatment options for migraine would need to take account of the other elements of resource utilization—especially primary care consultations—required by the management of the disorder.

## Conclusion

A challenging research agenda faces the clinical and economic evaluation of acute treatments for migraine. Nevertheless, from an economic perspective, the present study suggests that cost-effectiveness offers a helpful analytical framework for examining the relative value-for-money offered by the growing number of antimigraine medicines. More specifically, its application to an economic comparison of eletriptan and sumatriptan, reported here, indicates that the former treatment is associated with a lower cost per successfully treated attack. Thus, employing the SM1 measure of outcome (sustained pain-free), the cost per successfully treated attack for eletriptan 40 mg is 27% of that found for sumatriptan 50 mg. Comparing eletriptan 80 mg and sumatriptan 100 mg, the corresponding value is 39%. These results suggest that eletriptan has a potentially important contribution to make to the cost-effective management of migraine.

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